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Marked up copies of the amended claims that show the actual amendments are included as Appendix A.

REMARKS

The Specification has been amended at page 1, lines 2 to 8 in order to update the status of the parent of the present application. As such, the amendment does not constitute new subject matter.

Claims 1, and 12 to 19 have been cancelled. Claims 12 to 19 have been withdrawn from the present prosecution because they are directed to non-elected subject matter. Claim 1 is cancelled from the present prosecution, however, Applicants expressly reserves the right to pursue the subject matter of claim 1 in any future prosecution.

Claims 2, 3, and 11 have been amended to remedy certain informalities pointed out by the Examiner. The amended claims are fully supported by the present application, as no new subject matter was added. Applicants note that in claim 2, the instance where m is 0 has been deleted to make the claim consistent with the elected invention from the restriction requirement.

Claim 21 has been amended to correct the nomenclature of the claimed compound, support for this amendment is found in the specification, for example, on page 100, line 13 (item 112 of the list of compounds in Example XXXIX), therefore the amendment does not constitute new subject matter.

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Rejection Under 35 U.S.C. 112, First Paragraph

Claims 1 to 11 and 21 to 25 are rejected under 35 U.S.C. 112, first paragraph. It is alleged that enablement is lacking regarding how to make and use "the myriad" of claimed peptides which specifically inhibit the activity of Factor Xa. The rejection posed the question, "which or what is the common core amino acid sequence that would elicit said function to the claimed peptides?"

It is also alleged that the present specification fails to provide information that would allow the skilled artisan to practice the invention without undue experimentation. *In re Wands* is cited, and specifically the eight factors that are considered when determining if undue experimentation is required in order to practice the invention. Specifically the rejection alleges that "Applicants fail to set forth 'the common core' required in the peptide for eliciting the necessary function."

It is further alleged that claims 24 and 25, insofar as they read on a method of use to *in vivo* subject, are not enabled by the instant disclosure because there is no indication or showing that the compounds do specifically inhibit activity of Factor Xa under *in vivo* conditions.

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Response to Section 112, First Paragraph Rejections

Applicants respectfully submit that the claimed invention is enabled, and that a skilled artisan could practice the claimed invention without undue experimentation.

In reciting the Section 112, first paragraph rejection, the office action states that

Enablement is lacking regarding the how to make and use for the myriad of claimed peptides which are to "specifically inhibit the activity of Factor Xa". Which or what is the common core amino acid sequence that would elicit said function to the claimed peptides?

Regarding the query as to the "common core amino acid sequence," Applicants respectfully note that the elements of the claimed invention are fully recited in the claims, and are taught in the specification. For example, claim 2 teaches all of the structural elements that define the present invention. All the substituents are defined as to their points of attachment, and to the chemical groups that are included. As is evident from claim 2, the present invention is defined not in terms of a "common core amino acid sequence," but in terms of a compound with a peptide backbone that is variously substituted. The various substituent groups provide the "common core" of the present

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invention with the desired outcome that compounds substituted as taught exhibit the claimed utility.

Applicants note that the present specification includes fifty-three pages of disclosure that includes thirty-four working examples that teach the preparation and demonstrate the utility of the claimed invention. For instance, **Example I** teaches peptide synthesis procedures that were used in preparing the present invention. **Examples II to XXV**, and **XXXIV** (a total of twenty-five (25) working examples) recite the preparation of peptides of the present invention. Applicants note that these examples recite both the procedures used for preparing the peptides, and the analytical data related to the prepared compounds. **Examples XXVI to XXXIII** teach peptides belonging to the non-elected invention resulting from the restriction requirement, that is, compounds where $m=0$. Although **Examples XXVI to XXXIII** are directed to claims that are not included in the present prosecution, their teachings are nonetheless relevant as additional teachings about procedures and protocols useful for the preparation of peptides in general, and serve as further evidence of the breadth of the teachings of the present specification.

Example XXXV teach twenty-three (23) peptides with multiple substitutions that are potent inhibitors of factor Xa. **Example XXXVI** teaches two hundred and ninety-one (291) peptides that have K_i values between 100uM and 1pM for factor Xa inhibition.

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Example XXXVII teaches assays and procedures used for determining inhibition of factor Xa, thrombin, plasmin, elastase and trypsin. **Example XXXVIII** teaches assays and procedures used for determining inhibition of coagulation (in vivo dilute prothrombin time assay, and ex vivo dilute prothrombin time assay). **Example XXXVIII** also teaches forty-five (45) compounds that show at least 30% inhibition in 10 min in the ex vivo dilute prothrombin time assay following administration of less than or equal to 2 mg/kg of the compound; and thirteen (13) additional compounds that show at least 30% inhibition in the dilute prothrombin time assay following intra-duodenal administration of less than or equal to 50 mg/kg of a compound.

Example XXXIX teaches one hundred and thirteen (113) factor Xa inhibitors of the present invention with a K_i less than 100 μ M.

Applicants respectfully note that in just **Examples XXXV to XXXIX**, there are four hundred eighty-five (485) compounds taught. These compounds were prepared and assayed according to the procedures taught in the specification and examples. Applicants further note that these compounds are recited in the pending claims. As to the query regarding the "common core of the peptide sequence," Applicants respectfully refer to the previous discussion regarding this query. Applicants also submit that the number and variety of the above-referenced taught compounds fully support the common core of the invention as taught in claims. In summary, Applicants respectfully submit

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that the allegation that the claimed invention is not enabled is unfounded, and submit that the rejection should be withdrawn.

It is also alleged that the present invention cannot be practiced by a skilled artisan without undue experimentation as determined according to the factors recited in *In re Wands*. Applicants respectfully traverse. Application of the *Wands* factors to the present specification, shows that the present invention can, indeed, be practiced without undue experimentation.

For example regarding the **quantity of experimentation necessary to practice the invention**, Applicants submit that the present specification is well within the criteria recited in *Wands*. The preparation of the peptides of varying sizes and types are taught. Four Hundred and eighty-five (485) peptides that show activity are taught, these include peptides with single and multiple combinations of substitutions that show desired activity. The assays, including their procedures and experimental conditions used to determine the activity of the peptides, are taught. And the number working examples that teach compounds in the specification, as was previously discussed, more than satisfies this *Wands* factor

Regarding **the amount of direction and guidance provided**, as discussed above, the specification teaches all the procedures necessary to synthesize and assays the peptides of this invention. Additionally, the specification teaches peptides

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that have the desired activity, having various combinations of substitutions, and combinations of substitutions.

Regarding **the presence or absence of working examples**, also as previously noted, the specification provides thirty-nine working examples that teach the preparation and assaying of peptides of the claimed invention.

And regarding **the relative skill of those in the art**, the skilled artisan in this area of technology is high, generally with at least a graduate degree, and usually a doctorate in biochemistry, chemistry, or the like. Applicants submit that the skilled artisan in this art would be able to utilize the teachings of the specification to practice the claimed invention.

Applicants respectfully submit that the skilled artisan is able to practice the present specification without undue experimentation according to the factors stated in *In re Wands*, and respectfully submits that the aforementioned rejection should be withdrawn.

Rejection of Claims 24 and 25 Under 35 U.S.C. 112 First Paragraph

Regarding the allegation that claims 24 and 25, insofar as they read on a method of use to in vivo subject, are not enabled by the instant disclosure because there is no indication or showing that the compounds do specifically inhibit activity of Factor Xa under in vivo conditions. Applicants respectfully direct the Examiner's attention to MPEP §2107.02, Part I, **Special**

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**Considerations for Asserted Therapeutic or Pharmacological
Utilities**, which states,

As a general matter, evidence of pharmacological or other biological activity of a compound will be relevant to an asserted therapeutic use if there is a reasonable correlation between the activity in question and the asserted utility.

The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted.

emphasis added

As previously discussed, the working examples include Examples XXXVII and XXXVIII. Example XXXVII teaches factor Xa, thrombin, plasmin, trypsin, and elastase assays that were used to determine and demonstrate inhibition of Factor Xa. Example XXXVIII teaches an *in vitro* dilute prothrombin time assay, and an *ex vivo* dilute prothrombin time assay, that were used to determine inhibition of coagulation as an additional measure of factor Xa inhibition. As such, Applicants respectfully submit that the rejection to claims 24 and 25 are unfounded, and should be withdrawn.

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Rejection Under 35 U.S.C. 112, Second Paragraph

Claims 1 to 11 and 24 to 25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular the Office action has pointed out the following concerns.

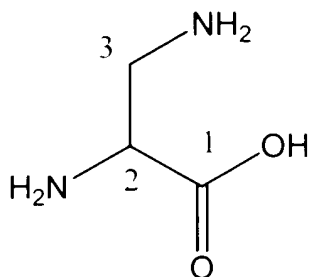
Regarding the rejection to claim 1, Applicants note that claim 1 has been cancelled, and therefore the rejections have been rendered moot.

Regarding the rejection to claim 2, Applicants have amended the claim according to the Examiner's helpful suggestions, and submit that claim 2, as amended, is in proper form for allowance.

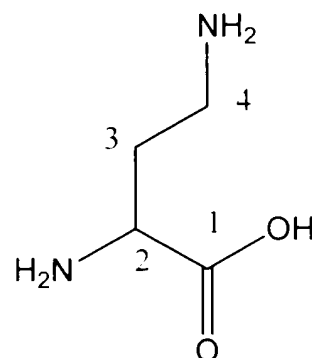
Regarding the rejection to claim 3, Applicants have amended the claim applying the suggestions the Examiner had made for claim 2, and submit that claim 3, as amended, is in proper form for allowance.

Regarding the rejection to claim 9, Applicants note that claim 9 does not include a compound with the structure "-Dah(CH=N(CH).)" Applicants further note that there is no disclosure in the present specification to the structure "Dah." There are teachings to the structures "Dab" and "Dap", which refer to 2,4-diaminobutyric acid (page 11, line 27), and 2,3-diaminopropionic acid (page 11, line 30), respectively.

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2,3-diaminopropionic acid



2,4-diaminobutyric acid

As depicted above, Applicants note that DAP and DAB are diamino substituted carboxylic acids that can form peptide bonds through their carbonyl carbon, methylene carbon, and the 2-substituted amino group with the remainder of the molecule constituting the side arm of the peptide residue. Regarding the Examiner's inquiry as to the "expanded structure" of the compound, Applicants understand the inquiry as to mean, how the "(CH=N(CH.)" is attached to DAP and DAB. Applicants respectfully submit that one of ordinary skill in the relevant art would know that the aforementioned group would be attached to the 3-amino group in DAP, or the 4-amino group in DAB.

Regarding the rejection to claim 21, Applicants have amended the claim in order to clarify structure of the compound. As indicated above, the amendment is supported in the

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specification and therefore does not constitute new subject matter. Applicants respectfully submit, that the claim as amended, is in proper form for allowance.

Rejection Under 35 U.S.C. 102 and 103

The Examiner has reinstated the rejection of claims 1 to 11 under 35 U.S.C. 102(a and/or b)/103(a) over Brunck and Marlow, which was originally raised in the office action of March 23, 2000. The reason given for the reinstatement was that under further consideration, it was noted that the present application is a CIP of the parent, and the priority date does not extend beyond the filing date of the present application, unless it can be shown that the claimed subject matter has been present in the earlier applications. The Office action further notes that the effective date for Brunck is December 15, 1993, which is the filing date of the Brunck parent application.

A review of the prosecution record shows that these issues were raised in the Office action mailed March 23, 2000, with the exception that there was no assertion that Brunck's priority dates back to December 15, 1993.

In Applicants' response to the Office action mailed March 23, 2000, it was stated that the full scope of claim 1 to 11 of the present application are taught in the parent application. Upon further review Applicants would like to clarify that while the present CIP application is not of greater breadth than its parent application, it does contain new subject

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matter, namely, the compounds that are taught in Example XXXIX, which as noted below is new to the present application. These compounds were taught generically in the parent application, and are encompassed within the breadth of the issued parent claims. However, their actual structures and relevant data are taught in the CIP.

In the present Office action, the Examiner further indicated that she has not been able to locate the parent files to the instant Application for purposes of comparing the new matter entered into the CIP, and urges the Applicants to clarify this matter in order to expedite the prosecution of the present Application.

Clarification of Disclosures Between Present Application and Parent Application

In response to the Examiner's request for clarification of new subject matter in the present continuation-in-part application from that of its parent, Applicants provide as follows, a listing of the disclosures that are new for the present application.

Page 1, lines 2 to 4

This paragraph contains subject matter that is not present in the parent application. However, Applicants note that the disclosure merely updates the status of the parent

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application, that is, stating that it has issued as U.S. Patent 5,849,510, and therefore the disclosure does not constitute new subject matter.

Page 28, line 13 to page 39, line 10

These pages recite support for claims 1, 2, 3, and 12. The majority of the claims are directed to compounds that were taught in the parent application, but not specifically claimed as individual species. There are also compounds that were generically taught in the parent application, and are now specifically taught in the present application. As indicated below, these compounds are listed in Example XXXIX.

Page 96, line 15 to page 100, line 14, Example XXXIX

This Example XXXIX teach additional compounds to those taught the '510 patent. Applicants note that the compounds of Example XXXIX are covered by claims to their genres in the '510.

Response to Rejections Under 35 U.S.C. 102 and 103

The effective priority date of the parent application is earlier than the effective date of Marlow, and therefore Marlow is not available as reference. Even if Marlow was available as a reference, the rejections still would not stand.

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Applicants previously presented these argument in their response mailed July 24, 2000, and respectfully submit that these argument still control. Rather than recite the arguments in their entirety, Applicants have attached as Exhibit A, a copy of the aforementioned Response mailed July 24, 2000, for the Examiner's convenience and review. As the response points out Marlow and Brunck, either individually or in combination, do not teach, or suggest the present invention.

Rejection Under 35 U.S.C. 101

Claim 11 is rejected under 35 U.S.C. 101 for claiming the same invention as in Claim 39, line 40 of U.S. Patent No. 5,349,510. Applicant submit that with the amendment of claim 11, this rejection is no longer applicable.

Obviousness Double Patenting Rejection

Applicants respectfully submit that the obviousness double patenting rejection should be held in abeyance until such time that the present claims are found allowable.

Amino Acid Sequence Listing Requirements

Applicants concur with the Examiner's suggestion that amendments to the application regarding SEQ ID Nos be held in abeyance until such time the pending claims are found allowable.

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CONCLUSION

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. Should the Examiner have any questions, he/she is invited to call Cathryn Campbell or the undersigned attorney.

Respectfully submitted,

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Date

James J. Wong
James J. Wong
Registration No. 34,949
Telephone No. (858) 535-9001
Facsimile No. (858) 535-8949

CAMPBELL & FLORES LLP
4370 La Jolla Village Drive
7th Floor
San Diego, California 92122
USPTO CUSTOMER NO. 23601



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APPENDIX A

In the Specification

The present application is a continuation-in-part of United States Serial No. 08/947,794 filed October 8, 1997 and issued as U.S. Patent 5,849,510, which is a continuation of prior application serial no. 03/428,404, filed April 25, 1995, which is a continuation-in-part of prior application serial no. 03/233,054, filed April 26, 1994, all of which are incorporated herein by reference.

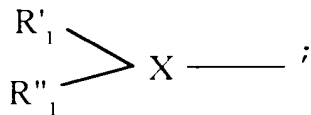
In the Claims

2. amended A non-naturally occurring compound that specifically inhibits the activity of factor Xa, having the general formula $A_1-A_2-(A_3)_m-B$, wherein m is ~~1 or 0~~;

wherein A_1 is $R_1-R_2-R_3$; A_2 is $R_4-R_5-R_6$; A_3 is $R_7-R_8-R_9$;

wherein

R_1 is



X is N;

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R' is selected from the group consisting of isobutyl, 1-methylpentyl, cyclohexylmethyl, cyclohexenylmethyl, 2-methylbutyl, -H and 2,3-dimethylpentyl;

R'' is selected from the group consisting of 2-benzofuroyl, alloc, acetyl, trifluoroacetyl, 2-quinolinoyl, 3-pyridoyl, 4-isoquinolinoyl, 5-benzylimidazolyl, 2-naphthylmethyl, 5-pyridiminoyl, benzoyl, 2-pyridoyl, tosyl, 3-quinolinoyl, 2-naphthylsulfonyl, 2-methylbenzyl, 2-furoyl, 3,4-dichlorobenzoyl, 2-thienylacetyl, N(5-methyl-2-thienyl), ethoxycarbonyl, 2-fluorobenzoyl, t-butoxycarbonyl, benzyl and 1-20 amino acids;

R₂ is -CR_{2A}R_{2B}-, wherein -R_{2A} and -R_{2B} are independently selected from the group consisting of -H, 4-amidinophenylmethyl, 4-aminophenylmethyl, 4-hydroxyphenylmethyl, 2-naphthylmethyl, 4-(N-methylpyridinyl)methyl, (3-iodo-4-aminophenyl)methyl, (4-aminocarbonylphenyl)methyl, (3-iodo-4-hydroxyphenyl)methyl, and (4-cyanophenyl)methyl, (4-hydroxyphenyl)methyl;

R₃ is -C(O)-;

R₄ is -NH-;

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R_5 is $-CP_{5A}R_{5B}$, wherein $-R_{5A}$ and $-R_{5B}$ are independently selected from the group consisting of $-H$, 2-butyl, and cyclohexyl;

R_6 is $-C(O)-$;

R_7 is $-NH-$;

R_8 is $-CP_{8A}R_{8B}$, wherein $-R_{8A}$ and $-R_{8B}$ are independently selected from the group consisting of $-H$, 3-guanypropyl, (dimethylamidinium)aminomethyl, (dimethylamidinium)aminoethyl, 3-(N-methylpyridinyl)methyl, and 4-(N-methylpyridinyl)methyl;

R_9 is $-C(O)-$; and

B is Leu-Pro-NH₂, Leu-Hyp-NH₂, Pen(CH₂COOH)-Pro-NH₂, Cys(CH₂COOH)-Pro-NH₂, γ -carboxyglutamic acid-Pro-NH₂, (N-carboxymethyl)Gly-Pro-NH₂, (N-carboxyethyl)Gly-Pro-NH₂, (N-1,3-dicarboxypropyl)Gly-Pro-NH₂, (N-methyl)Leu-Pro-NH₂, Leu-NH₂, Leu-OH, $-NH-(4\text{-trimethylammoniumbenzyl})$, $-NH-[4\text{-(1-methylpyridinium)methyl}]$, and $-NH-(4\text{-amidinobenzyl})$.

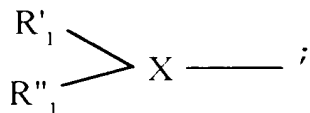
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3. amended A non-naturally occurring compound that specifically inhibits the activity of factor Xa, having the general formula $A_1-A_2-(A_3)_m-B$, wherein m is 1;

wherein A_1 is $R_1-R_2-R_3$; A_2 is $R_4-R_5-R_6$; A_3 is $R_7-R_8-R_9$;

wherein

P_1 is



X is N;

R'_1 is selected from the group consisting of H, isobutyl, 2-methylpentyl, cyclohexylmethyl, 3-quinolinyl, 2-methylbutyl, 2,3 dimethyl pentyl, and cyclohexenylmethyl;

P''_1 is selected from the group consisting of 2-benzofuroyl, alloc, acetyl, trifluoroacetyl, 2-quinolinoyl, 3-pyridoyl, 4-isoquinolinoyl, 5-benzimidazolyl, 2-naphthylmethyl, 5-pyrazinoyl, benzoyl, 2-pyridoyl, tosyl, 3-quinolinoyl, 2-naphthylsulfonyl, 2-methylbenzyl, and benzyl;

R_1 is $-CF_{12}R_{12}$, wherein $-R_{12}$ and $-R_{13}$ are independently selected from the group consisting of H, 3-

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amidinophenylmethyl, 4-amidinophenylmethyl,
4-aminophenylmethyl, 4-hydroxyphenylmethyl, 2-
naphthylmethyl, 4-(N-methylpyridinyl)methyl,
(3-iodo-4-aminophenyl)methyl,
(4-aminocarbonylphenyl)methyl,
(3-iodo-4-hydroxyphenyl)methyl,
(4-cyanophenyl)methyl, and 3-indolylmethyl;

P_3 is selected from the group consisting of $-C(O)-$, $-CH_2-$, $-CHR_{35}-C(O)-$ and $-C(O)-NR_{35}-CH_2-C(O)-$,
wherein R_{35} is the CHR_{35} group of the bridging
group $-C(O)-CR_{35}-$;

P_4 is $-NH-$;

P_5 is $-CR_{5A}R_{5B}$, wherein $-R_{5A}$ and $-R_{5B}$ are independently
selected from the group consisting of $-H$, 2-butyl, cyclohexyl
and phenyl;

P_6 is $-C(O)-$;

P_7 is $-NH-$;

P_8 is $-CR_{8A}R_{8B}$, wherein $-R_{8A}$ and $-R_{8B}$ are independently
selected from the group consisting of $-H$,
3-guanylpropyl, (dimethylamidinium)aminomethyl,
(dimethylamidinium)aminoethyl,
3-(N-methylpyridinyl)methyl,
N(carboxymethyl)(3-pyridinylmethyl), and

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4-(N-methylpyridinyl)methyl;

R₃ is selected from the group consisting of -C(O)-, -CH₂- and -CHR₉₉-C(O)-; and

B is -NH₂, -OH, Leu-Pro-NH₂, Leu-Hyp-NH₂,
Pen(CH₂COOH)-Pro-NH₂, Cys(CH₂COOH)-Pro-NH₂,
γ-carboxyglutamic acid-Pro-NH₂,
(N-carboxymethyl)Gly-Pro-NH₂,
(N-carboxyethyl)Gly-Pro-NH₂,
(N-1,3-dicarboxypropyl)Gly-Pro-NH₂,
(N-methyl)Leu-Pro-NH₂, Leu-NH₂, and Leu-OH.

11. (amended) A compound selected from the group consisting of

Alloc-pAph-Chg-Pal(3)Me-NH₂;
(2-quinolinoyl)-pAph-Chg-Pal(3)Me-NH₂;
Ac-pAph-Chg-Pal(3)Me-NH(1-methoxycarbonyl)
-1-cyclohexyl;
Ac-pAph-Chg-Arg-NH₂;
(2-pyridoyl)-pAph-Chg-Pal(3)Me-NH₂;
CF₃C(O)-(iBu)Phe(pNH₂)-Chg-Arg-NH₂;
Ac-pAph-Chg-Pal(3)Me-NH-(1-methoxycarbonyl)
-1-cyclopentyl;
Ac-pAph-Chg-Pal(3)Me-NH-(4-methoxycarbonyl
-cyclohexyl)methyl;
Ac-pAph-Chg-Pal(3)Me-NH-(3-thienyl-2
-carboxylic acid methyl ester);
Ac-pAph-Chg-Arg-NH₂;

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$\text{CF}_3\text{C}(\text{O})-(\text{iBu})\text{Tyr}-\text{Chg}-\text{Arg}-\text{OH};$

$\text{Ac-pAph}-\text{Chg}-\text{Pal}(3)\text{Me}-\text{NH}-(4\text{-methoxycarbonyl}$
 $\text{-cyclohexyl)methyl};$

$\text{Ac-pAph}-\text{Chg}-\text{Pal}(3)\text{Me}-\text{NH}_2;$

~~$\text{Ac-pAph}-\text{Pgl}-\text{Pal}(3)\text{Me}-\text{NH}_2;$~~

$\text{Ac-pAph}-\text{Chg}-\text{Pal}(3)(\text{CH}_2\text{COOH})-\text{NH}_2;$

$(2\text{-quinolinecarboxy})-\text{pAph}-\text{Chg}-\text{Pal}(3)\text{Me}-\text{NH}_2;$

$\text{Ac-pAph}-\text{Chg}-\text{Pal}(3)\text{Me}-\text{NH}-(4\text{-carboxycyclohexyl})$
 $\text{methyl}; \text{ and}$

$\text{CF}_3\text{C}(\text{O})(\text{iBu})-\text{Tyr}-\text{Ile}-\text{Arg}-\text{NH}_2.$

21. (amended) A compound $\text{Ac-D-pAph}-\text{Chg}-\text{Pal}(\underline{3})\text{Me}-\text{Leu}-\text{Pro}-\text{NH}_2.$